UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,766	05/10/2006	Thomas A. Beyer	PC25123A	6301

28523 7590 06/03/2008

PFIZER INC.
PATENT DEPARTMENT, MS8260-1611
EASTERN POINT ROAD
GROTON, CT 06340

EXAMINER	
JAISLE, CECILIA M	

ART UNIT	PAPER NUMBER
1624	

NOTIFICATION DATE	DELIVERY MODE
06/03/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

~IPGSGro@pfizer.com

Office Action Summary	Application No.	Applicant(s)	
	10/595,766	THOMAS A. BEYER	
	Examiner	Art Unit	
	CECILIA M. JAISLE	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,12-14,16-18,20 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-5, 16, 17 and 21* is/are allowed.

6)☒ Claim(s) *6-8,12-14,18 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Lack of Unity

Applicants' election of Group I without traverse in the Response of Dec. 13, 2007 is acknowledged. Claims 1-8, 12-14, 16-18, 20 and 21, all claims in this application, drawn to pyrido[2,3-d]pyrimidine compounds, pharmaceutical compositions comprising them and pharmaceutical methods using them, are under examination on their merits.

Rejections Under 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-8, 12-14, 18 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for a method of treatment of bone fracture, bone defect and promotion of bone in-growth in mammals. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims. **The previously indicated allowability of methods of treatment of bone fracture or bone defect and promotion of bone in-growth in mammals is withdrawn.** The following reasoning applies to this rejection.

Many factors require consideration when determining whether sufficient evidence supports a conclusion that a disclosure satisfies the enablement requirement and

whether any necessary experimentation is "undue." MPEP 2164.01(a). These factors include: (1) the claim breadth; (2) the nature of the invention; (3) the state of the prior art; (4) the level of predictability in the art; (5) the amount of direction provided by the inventor; (6) the presence of working examples; and (7) the quantity of experimentation needed to use the invention based on the content of the disclosure. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)(reversing the PTO's determination that claims directed to methods for hepatitis B surface antigen detection did not satisfy the enablement requirement). See also *In re Goodman* 29 USPQ2d 2010, 2013 (Fed.Cir. 1993). Application of these factors to the present application supports the determination that the present disclosure fails to satisfy the enablement requirement:

1. **Breadth of the claims:**

(a) Scope of the compounds. The claims cover potentially millions of compounds of Formula (I). When EP2 selective receptor agonists are added, the potential compositions grow to the billions.

(b) Scope of the diseases covered. The scope of the claims has been discussed above.

The scope of bone defects is immense. The term includes common bone defects such as Paget's disease, hereditary multiple exostosis and osteoporosis. It also includes Dysplasias including Osteogenesis imperfecta, Osteopoikilosis, Osteopetrosis (Albers-Schoenberg disease), achondroplasia, Osteochondromatosis, Caffey's disease, Lenz-Majewski syndrome, Melorheostosis, metaphyseal dysplasia (Pyle disease), pyknodysostosis, sclerosing diaphyseal dysplasia (Camurati-

Engelmann Disease), spondyloepiphyseal dysplasia and many others. It includes dense bones defects, including axial osteomalacia, fibrogenesis imperfecta ossium, sarcoidosis and tuberous scelrosis. Other bone defects include cleidocranial dysostosis, coxa plana, Hand-Schueller-Christian disease, brachydactyly, calcium pyrophosphate deposition disease (CPPD), Wormian bones, tibia vara (Blount disease), cervical spine fusion (ankylosis), Crouzon syndrome, slipped capital femoral epiphysis (SCFE), celery-stalk metaphyses, Bankart deformity, Ollier disease, craniosynostosis, Erlenmeyer flask deformity, ivory vertebral body, spheroid calcification, acro-osteolysis, Caffey disease, cherubism, Sever disease, Sprengel deformity, Panner disease, osteogenesis imperfecta, Letterer-Siwe disease, Pott's disease, Scheuermann disease, sabre-shin deformity, basilar invagination, degenerative disc disease, block vertebra, Kohler disease, hyperostosis frontalis interna, diastrophic dwarfism, osteochondrosis, posterior vertebral scalloping, multicentric reticulohistio-cytosis, osteitis fibrosa, vertebra plana, Hill-Sachs deformity, Kienbock disease, spontaneous osteolysis, Osteochondritis dissecans, Osteomyelitis and many more. Included also are bone tumors, including Osteosarcomas (osteoblastic, chondro-blastic, fibroblastic, telangiectatic, and others), Hemangio-sarcoma, Periosteal chondrosarcoma, Periosteal fibrosarcoma, Maxillary fibrosarcoma, Parosteal osteosarcoma, Periosteal osteosarcoma, Malignant mesenchymoma, Liposarcoma, synovial sarcoma, Osteochondroma, Hemangioma, Myxoma of the jaw, Ossifying fibroma, Osteoma, Giant cell tumor of bone, multiple myeloma, solitary myeloma, reticulum cell sarcoma, malignnant fibrous histiocytoma, desmoblastic fibroma of the bone, periosteal

fibroma, lipoma, Hemangioendothelial sarcoma, Ewing's sarcoma, chondroblastoma and Multilobular tumor of bone. There are also tumor-like lesions, including osteoid Osteoma, non-osteogenic Fibroma, benign osteoblastoma, Solitary bone cyst, Juxta-cortical bone cyst, Myositis ossificans, Villonodular synovitis and Epidermoid cyst of the phalanx. There are also secondary malignant bone deposits.

The specification fails to identify the results of treatment with the compounds of this invention and how such results would be recognized.

2. **Nature of the invention and predictability in the art:** The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

Pharmacological activity in general is unpredictable. In applications involving physiological activity, such as the present:

> The first paragraph of 35 U.S.C. §112 effectively requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

Plant Genetic Systems v. DeKalb Genetics, 65 USPQ2d 1452, 1456 (Fed.Cir. 2003).

3. **Direction and Guidance:** That provided is very limited. The dosage range information is meager at best. It is generic, the same for all disorders the specification covers. No specific direction or guidance provides a regimen or dosage effective specifically for all of the conditions construed by the claims.

4. **State of the prior art:** These compounds are amino pyrido[2,3-d]pyrimidines with a particular substitution pattern. No amino pyrido[2,3-d]pyrimidines of any kind have been used for treatment of the bone defects here described.

5. **Working Examples:** The examples only show treatment of bone fracture and promotion of bone in-growth in rats with the compounds of Examples 1-37. Applicants do not provide highly predictive competent evidence or recognized tests to treat all bone conditions construed by the claimed compounds.

6. **Skill of those in the art:** With regard to osteoporosis, bone fracture and/or defect, delayed or non-union fracture, spinal fusion, bone in-growth, cranial facial reconstruction, Bonnet, et al., Toxicology and Applied Pharmacology, 221 (2007), 111-118, report that "serious issues have been raised regarding the potential use of PDE inhibitor for bone treatment. ... [T]he complexity of PDE inhibitors action on bone cells and the lack of *in vivo* data require further study." Bonnet further suggests combinations of different PDE inhibitors ("...a combination of PDE4 and PDE2 inhibitors is more efficient that a specific PDE4 inhibitor"), and the report concludes, "However, clinical trials as well as further basic studies will be needed to substantiate the efficacy of PDE inhibitors..." Regarding any relationship between PDE2 inhibition and osteoporosis, Bonnet, at p. 115, "... noted a higher beneficial effect of tofisopam compared to rolipram, suggesting a role of PDE4 but also of PDE2 in the bone metabolism." Regarding any relationship between PDE2 inhibition and bone fracture, bone defect, Bonnet, p. 117, suggested that PDE4, PDE3 and

PDE2 inhibitors "are potential new candidates for osteoporosis treatment," while recognizing some limitations of their study:

> First we have not compared the antidepressant treatments with classic anti-osteoporotic treatment ... to know if some antidepressants can also protect from bone deterioration as well as anti-osteoporotic treatments. Secondly histomorphometric data would be useful to better understand the effect on bone remodeling, and confirm the bone markers data.

Note also that Elefteriou, Cell. Mol. Life Sci. 62(2005)2339-2349, observed the anomaly, "Among all PDEs, PDE4 was demonstrated to be responsible for the induction of *RankI* expression in osteoblasts. However, PDE inhibitors injected daily in vivo had an anabolic effect, induced EFK1/2 and P38 MAPK and increased osteoblast differentiation, but did not significantly affect resorption parameters."

7. **Quantity of experimentation needed to make or use the invention.** Based on the disclosure's content, an undue burden would be placed on one skilled in the pharmaceutical arts to make and use the invention, since the disclosure gives the skilled artisan inadequate guidance regarding pharmaceutical use, for reasons explained above. The state of the art, as discussed in the articles referenced above, indicates the requirement for undue experimentation. Thus, the ability of an agent that inhibits PDE-2 to ameliorate all of the bone diseases/conditions/symptoms recited by the present claims remains open to further study and proof.

Substantiation of utility and its scope is required when utility is "speculative," "sufficiently unusual" or not provided. See *Ex parte Jovanovics, et al.*, 211 USPQ 907, 909 (BPAI 1981). Also, note *Hoffman v. Klaus*, 9 USPQ2d 1657 (BPAI 1988) and *Ex parte Powers*, 220 USPQ 924 (BPAI 1982) regarding types of testing needed to support *in vivo* uses. Applicants' attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 66 FR 1092-1099 (2001), emphasizing that "a claimed invention must have a specific and substantial utility." See also MPEP 2163, *et. seq*. The disclosure in this application is not sufficient to enable the instantly claimed methods based solely on disclosure of inhibition of PDE-4 by compounds of Formula (I).

MPEP 2164.01(a) states,

> A conclusion of lack of enablement means that, based on the evidence regarding each of the above [Wand] factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed.Cir. 1993).

The above consideration clearly justifies that conclusion here and undue experimentation would be required to practice Applicants' invention. The consideration of the above factors demonstrates that the present application does not sufficiently enable the present claims. In view of the pharmaceutical nature of the invention, the unpredictability of relationship between PDE-2 and specific diseases/conditions, one of ordinary skill in this art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

Allowed Claims

Claims 1-5, 16, 17 and 21 are allowed. An examiner's statement of reasons for indication of allowed claims can be found in the Office Action of Feb. 6, 2008.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CECILIA M. JAISLE, J.D. whose telephone number is (571)272-9931. The examiner can normally be reached on Monday through Friday; 8:30 am through 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

CECILIA M. JAISLE, J.D.

5/19/2008

/James O. Wilson/

Supervisory Patent Examiner, Art Unit 1624